E2C(R2) Periodic Benefit-Risk Evaluation Report

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INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER)

E2C (R2)

Current *Step 2* version

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1 INTRODUCTION

The Periodic Benefit-Risk Evaluation Report (PBRER) described in this guideline is intended to be a common standard for periodic benefit-risk evaluation reporting on marketed products (including approved drugs that are under further study) among the ICH regions. Regulators from EU, Japan, and the US believe that the PBRER may be used to meet prevailing national and regional requirements for periodic safety and/or benefit-risk reports for approved medicinal products.

This guideline defines the recommended content and format of a PBRER and provides an outline of points to be considered in its preparation and submission.

Definitions of many technical terms used in the guideline are included in a glossary (Appendix A); the first mention of a term in the guideline is identified with an asterisk (*).

1.1 Background

When a new medicinal product is approved for marketing, demonstration of safety and efficacy are generally based on data from a limited number of patients, many studied under the controlled conditions of randomised trials. Often, higher risk subgroups and patients with concomitant illnesses that require use of other drugs are excluded from clinical trials, and long-term treatment data are limited. Moreover, patients in trials are closely monitored for evidence of adverse events. In clinical practice, monitoring is less intensive, a broader range of patients are treated (age, co-morbidities, drugs, genetic abnormalities), and events too rare to occur in clinical trials may be observed (e.g., severe liver injury). These factors underlie the need for continuing analysis of relevant safety, efficacy,[1] and effectiveness[1] information throughout the lifecycle of a medicinal product – promptly, as important findings occur – and periodically, to allow an overall assessment of the accumulating data. Although the majority of new information will be safety-related, new information about effectiveness, limitations of use, alternative treatments, and many other aspects of the drug's place in therapy may be pertinent to its benefit-risk assessment.

The ICH Guideline E2C, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, achieved Step 4 in 1996, and was intended to harmonise the periodic reporting requirements to regulatory authorities and to provide, in a common format, the worldwide safety experience of a medicinal product at defined times post-approval. At that time, the focus of the Periodic Safety Update Report (PSUR) was on relevant new safety information in the context of patient exposure, to determine if changes were needed to the product information in order to optimise the use of the product. The guideline was revised in 2003, to provide needed clarification, as well as to provide additional guidance and flexibility.

The pharmacovigilance environment has evolved, however, prompting reassessment of the role of the PSUR in the spectrum of safety documents submitted to regulatory authorities. This reassessment highlighted several factors that led to consensus for revision and refocus of the guideline, to enhance its usefulness in light of advances in the field:

[1] The terms efficacy and effectiveness are not standardised, and have different meanings in some regions.

- significant progress in the technology and science of pharmacovigilance, including electronic submission of individual case safety reports (ICSRs) to regulatory authorities, automated data mining techniques, and more attention to benefit-risk evaluation;
- greater emphasis on proactive and documented risk management planning;
- increasing recognition that meaningful evaluation of important new risk information should be undertaken in the context of a medicinal product's benefits; and
- overlap in the content of ICH guidelines related to pharmacovigilance documentation, particularly between ICH guideline E2C, the safety specification component of ICH guideline E2E, and ICH guideline E2F, the Development Safety Update Report (DSUR).

As noted above, the primary objective of the PSUR was to provide a comprehensive picture of the safety of approved medicinal products. With recognition that the assessment of the risk of a medicinal product is most meaningful when considered in light of its benefits, the proposed report would provide greater emphasis on benefit than the PSUR, particularly when risk estimates change importantly. In such cases there will need to be an overall explicit evaluation of benefit-risk. Consequently the name of the proposed report is the "Periodic Benefit-Risk Evaluation Report" (PBRER). The PBRER would also provide greater emphasis on the cumulative knowledge regarding a medicinal product, while retaining a focus on new information.

A formal evaluation of benefit is a new feature of the PBRER; however, it is recognised that a concise discussion of benefit will usually be sufficient, unless the safety or benefit-risk profile has changed significantly during the reporting interval. Thus, the level of detail provided in certain sections of the PBRER (e.g., evaluation of safety and efficacy data, evaluation of safety signals,* and benefit-risk evaluation) should be proportional to the medicinal product's known or emerging important risks and to evidence of emerging important benefits.

The frequency of submission of reports to regulatory authorities is subject to national or regional regulatory requirements, and may differ, depending on a number of factors. The guideline includes specific advice on managing different frequencies of PBRER submission in different regions.

The PBRER has been developed in such a way that the content of particular sections of the report could be identical to that of corresponding sections of other regulatory documents, specifically the safety specification described in the ICH guideline E2E and the DSUR described in ICH guideline E2F. Thus, the content of these sections of the PBRER is envisioned to be suitable for use in the other reports. This "modular approach*" would allow sections or modules to be submitted at different times to multiple authorities, across separate documents (i.e., the PBRER, DSUR, and safety specification). Only modules that include new information would need to be updated when submitting the PBRER. This approach is expected to improve efficiency for marketing authorisation holders (MAHs) and regulatory authorities in their preparation and review of these documents, respectively.

1.2 Objectives

The main objective of a PBRER is to present a comprehensive and critical analysis of new or emerging information on the risks of the medicinal product, and, where pertinent, on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile. The PBRER should be submitted to regulatory authorities, and will contain an evaluation of new information relevant to the medicinal product that became available to the MAH during the reporting interval, in the context of cumulative information by:

- examining whether the information obtained by the MAH during the reporting interval is in accord with previous knowledge of the medicinal product's benefit and risk profile;
- summarising relevant new safety information that could have an impact on the benefit-risk profile of the medicinal product;
- summarising any important new efficacy/effectiveness information that has become available during the reporting interval; and
- where important new safety information has emerged, conducting an integrated benefit-risk evaluation for approved indications.

When desired by the MAH, a list of the sources of information used to prepare the PBRER can be provided as an appendix to the report.[2]

A PBRER should be concise and provide sufficient information to assure regulatory authorities that the MAH is adequately monitoring and evaluating the evolving risk profile of a medicinal product. All pertinent new safety information discovered during the reporting interval[3] should be discussed in the appropriate sections of the PBRER. Urgent safety information should be reported through the appropriate mechanism; the report is not intended to be used to provide initial notification of significant new safety information or to provide the means by which new safety concerns* are detected.

1.3 Scope of the PBRER

The main focus of each PBRER is the evaluation of relevant new safety information from the available data sources,[3] placed within the context of any pertinent efficacy/effectiveness information that may have become available since the International Birth Date (IBD), the date of the first marketing approval in any country in the world, or the Development International Birth Date (DIBD), the date of first authorisation for the conduct of an interventional clinical trial in any country.[4] The PBRER should include cumulative knowledge of the product while retaining focus on new information, i.e., the overall safety evaluation and integrated benefit-risk evaluation will take into account cumulative information. Because clinical development of a drug frequently continues following marketing approval, relevant

[2] Examples of potential sources of information to be used in preparation of a PBRER will be included in the Step 4 guideline as general guidance.

[3] This guideline should not serve to limit the scope of information to be provided in the evaluation of benefit-risk of a medicinal product. Please refer to the applicable laws and regulations in the countries and regions in which the PBRER is to be submitted.

[4] For the purpose of this document, the terms "authorisation" and "authorised" refer to clinical trials and the terms "approval" and "approved" refer to marketing applications.

information from post-marketing studies or clinical trials in unapproved indications or populations should also be included in the PBRER. Similarly, as knowledge of the safety of a medicinal product may be derived from evaluation of data associated with uses other than the approved indication(s), such knowledge would be reflected in the risk evaluation, where relevant and appropriate.

The PBRER should provide summaries of significant safety, efficacy/effectiveness information from data sources available to the MAH, when relevant to the benefit-risk evaluation.

1.4 Relation of the PBRER to Other ICH Documents

At present, some ICH countries and regions accept submission of separate types of periodic reports to fulfil national and regional requirements within the post-approval period: the PSUR (ICH guideline E2C(R1)) for periodic reporting of the safety of approved medicinal products, the DSUR (ICH guideline E2F) for periodic reporting on the safety of medicinal products that remain in clinical development, and the safety specification component of ICH guideline E2E that might be submitted at the time of marketing application and/or PSUR submission to aid in the planning of pharmacovigilance activities. As these documents have different regulatory purposes, different periodicities, and can be reviewed by different divisions within a single regulatory authority, each document needs to be complete in its own right – a comprehensive document that can stand alone. Nevertheless, overlap and repetition between the content of the DSUR, PSUR, and safety specification can lead to inefficiencies – both in the production of the documents by the MAH, and in the review of the documents by regulatory authorities. This guideline aims to address this duplication and facilitate flexibility by encouraging the use of individual modules, where they pertain to more than one report – to be used at different times, for different authorities, and for different purposes. Therefore, the PBRER has been developed in such a way that content of several sections may be used for sections of other documents as a basis for a modular approach (see Section 1.1).

2 GENERAL PRINCIPLES

2.1 Single PBRER for an Active Substance

The PBRER should provide information on all approved indications, dosage forms, and regimens for the active substance, with a single data lock point. In some circumstances, it will be appropriate to present data by indication, dosage form, dosing regimen, or population (e.g., children vs. adults) within the relevant section(s) of the PBRER. In exceptional cases, submission of separate PBRERs might be appropriate, for example, an active substance used in two formulations for systemic and topical administration in entirely different indications. In these cases, the regulatory authorities should be notified and their agreement obtained, preferably at the time of approval.

2.2 PBRERs for Fixed Dose Combination Product

For combinations of substances also marketed individually, information for the fixed combination may be reported either in a separate PBRER or included as separate presentations in the report for one of the individual substances, depending on the circumstances. Cross-referencing all relevant PBRERs is considered important.

2.3 Products Manufactured and/or Marketed by More than One Company

Each MAH is responsible for submitting PBRERs for its own products.

When companies are involved in contractual relationships (e.g., licensor-licensee), respective responsibilities for preparation and submission of the PBRER to the regulatory authorities should be clearly specified in the written agreement.

When data received from a partner company(ies) might contribute meaningfully to the safety and/or benefit-risk analyses and influence the reporting company's product information, these data should be included and discussed in the PBRER.

2.4 Reference Information

An objective of a PBRER is to evaluate whether information obtained during the reporting interval is in accord with previous knowledge on the product's benefit and risk, and to indicate whether changes should be made to product information. Reference information is needed to perform this comparison. Having one reference source of information in common for the three ICH regions would facilitate a practical, efficient, and consistent approach to the safety evaluation and make the PBRER a unique report accepted in all countries and regions.

It is a common practice for MAHs to prepare their own "Company Core Data Sheet,*" CCDS, which covers material relating to safety, indications, dosing, pharmacology, and other information concerning the medicinal product. The core safety information contained within the CCDS is referred to as the "Company Core Safety Information,*" CCSI. The latest CCDS in effect at the end of the reporting interval should be used as the reference for both the benefit and risk sections of the PBRER. The national or regional approved product information, which can differ from the CCDS, continues to be the reference document upon which labeledness/expectedness is based for the purpose of national or regional expedited post-marketing safety reporting.

It is important to highlight any differences between the CCSI and the national or regional product information/labelling in the cover letter or a regional appendix accompanying submission of the PBRER.

The MAH should continuously evaluate whether any revision of CCDS/CCSI is needed whenever new safety information is obtained throughout the reporting interval. All changes to the CCDS/CCSI made during the interval should be described in Section 4 ("Changes to Reference Safety Information*") and/or Section 16 ("Signal and Risk Evaluation") of the PBRER. The MAH should provide a copy of the current version of the CCDS(s) referred to in the PBRER as an appendix to the report.

2.5 Level of Detail within PBRER

The level of detail provided in certain sections of the PBRER should depend on the medicinal product's known or emerging important benefits and risks. This approach is applicable to those sections of the PBRER in which there is evaluation of safety data, efficacy/effectiveness data, safety signals, and benefit-risk. Therefore, the extent of information provided in such PBRER sections will vary among individual PBRERs.

For example, when there is important new safety information, a detailed presentation of that information should be included, plus any other relevant contextual information (e.g., updated full benefit information) needed to facilitate a robust benefit-risk analysis. Conversely, when little new important safety information has become

available during the reporting interval, a concise summary of baseline benefit information should be sufficient, and the benefit-risk evaluation would consist primarily of an evaluation of updated interval safety data, with the recognition that the benefit-risk profile has not changed during the reporting interval.

2.6 Benefit-Risk Evaluation

When a drug is approved for marketing, a conclusion has been reached that, when used in accordance with approved product information, its benefits outweigh its risks. As new information about the drug emerges during marketing experience, benefit-risk evaluation should be carried out to determine whether benefits continue to outweigh risks, and to consider whether steps need to be taken to improve the benefit-risk relationship through risk minimisation activities,* e.g., labelling changes, communications with prescribers, or other steps.

This assessment may include evaluation of populations and/or endpoints that were not investigated in the registrational clinical trials.

2.7 Periodicity and PBRER Data Lock Point

2.7.1 International Birth Date and Data Lock Point

The date of the first marketing approval for the medicinal product in any country in the world is the IBD. For medicinal products that are on the market in many countries, it is possible that there are several national or regional birthdates. Such different birthdates should be harmonised with the IBD with agreement of regulatory authorities. Through PBRERs prepared with harmonised IBDs, the same updated safety and benefit-risk information can be reviewed globally by all regulatory authorities.

The data lock point is the date designated as the cut-off for data to be included in a PBRER, based on the IBD. For administrative convenience, if desired by the MAH, the data lock point of the PBRER can be designated as the last day of the month of the end of the reporting interval, with a corresponding change to the start date of the next reporting interval. When a report contains information on different dosage forms, formulations, or uses (indications, routes and/or populations), which might be approved at different times, the original IBD should be maintained to determine the data lock point for purposes of the unified PBRER.

When clinical development of a medicinal product continues following marketing approval, the starting point of the DSUR reporting interval can be synchronized with the IBD-based cycle, so that both the DSUR and PBRER can be prepared at the same time.

2.7.2 Managing Different Frequencies of PBRER Submission

The need for the submission of a PBRER and the frequency of report submission to regulatory authorities are subject to national or regional regulatory requirements, and usually depend on such factors as the length of time the product has been on the market and the extent of knowledge of the benefit-risk profile of the product. During the initial years of marketing of new molecular entities (NMEs), reports will generally be requested more frequently (i.e., 6-monthly or annually). Once a drug has been marketed for several years, national or regional regulation may allow the frequency of submission to be extended to longer time intervals; however, more frequent PBRERs may continue to be required in other regions. As a result, the following

circumstances give some indication of the various scenarios that may be encountered by MAHs:

- Because approval dates and/or reporting frequency requirements differ across regions, PBRERs may be required on 6-monthly, annual, and less frequent submission timetables simultaneously across many regions.
- In some countries or regions, for products considered to have an established and acceptable safety profile or considered to be low risk, the frequency of reporting may be reduced, or the need to submit periodic reports may be eliminated completely. Even in such cases, where PBRERs are no longer required to be submitted, it is expected that MAH's will continue to evaluate the safety of their products on a regular basis and report any new safety information that impacts on the benefit-risk profile or the labelling of the product.
- Changes in reporting frequency may also apply after important additions or changes in clinical use are approved (e.g., new indication[s] and/or new population[s]), if such changes are regarded as having the potential to impact the benefit-risk profile of the product. In these circumstances, it is possible that the reporting interval will be shortened, even for older products with a previously reduced frequency of PBRER submission.
- An ad hoc PBRER may be requested by a regulatory authority (see Section 2.7.3.2 of this guideline)

As a result, the MAH may need to prepare PBRERs covering different intervals for different regulatory authorities.

It is anticipated that the "modular approach" introduced in this guideline will facilitate management of different frequencies of PBRER submission, and enhance the consistency and quality of the PBRER (see Section 1.1).

Independent of the length of the interval covered by the report:

- To the extent permitted under national or regional regulatory requirements, regulatory authorities may accept periodic reports based on the IBD of the product, using the content and format described in this guideline. Use of a single harmonised IBD for each product is important in order to reduce the burden of work involved in preparing PBRERs, and respects the original purpose of the PBRER – to prepare a single worldwide summary on a product that can be submitted to regulatory authorities.
- For newly approved products, a 6-monthly periodicity applies in many regions, for at least the first 2 years after an NME is approved.
- For PBRERs submitted on a routine/regular basis, the reports should be based on cumulative data, with interval data sets of 6 months, or multiples thereof.
- Whereas sections that provide interval information are likely to need to be updated, the content used in the previous PBRER module can be reviewed and reused for sections where no new information has arisen since preparation of the last PBRER, if appropriate. Specifically, sections that provide evaluation of cumulative data may not need to be updated (see Section 2.7.3.2, Figure 1; Appendix D).

2.7.3 PBRERs When Periodicity Differs Across Regions

When the MAH needs to prepare PBRERs covering different intervals for different regulatory authorities, the following approach should be used, and will eliminate the need for Summary Bridging Reports and Addendum Reports. Summary Bridging Reports and Addendum Reports, introduced in ICH guideline E2C(R1), should no longer be submitted.

Each PBRER should be a stand-alone document; the format and table of contents of all reports should be as described in this guideline. Regardless of the duration of the interval covered, each report should include interval data for the period covered, as well as cumulative data.

2.7.3.1 PBRERs with Data Lock Points Based on the International Birth Date

For two or more PBRERs that have the same data lock point but cover different durations, the cumulative sections of the PBRERs will be the same, whereas the interval sections may differ (see Section 2.7.3.2, Figure 1).

The cumulative data sections from the most recent PBRER can be submitted, along with updated interval data in the following sections, as appropriate:

- Actions Taken in the Reporting Interval for Safety Reasons (3.3)
- Changes to Reference Safety Information (3.4)
- Summaries of Significant Safety Findings from Clinical Trials during the Reporting Period (3.7)
- Findings from Non-interventional Studies* (3.8)
- Information from Other Clinical Trials and Sources (3.9)
- Non-clinical data (3.10)
- Literature (3.11)
- Other Periodic Reports (3.12)
- Lack of Efficacy in Controlled Clinical Trials (3.13)
- Late-Breaking Information (3.14)

For signal evaluation, MAHs should review the relevant sections from individual PBRERs covering the reporting interval, and incorporate the most recent information for each signal newly identified,* ongoing,* or closed* during that reporting interval.

For newly identified information on risk and efficacy/effectiveness, the MAH should review the relevant sections from individual PBRERs covering the reporting interval, and incorporate into the PBRER any new information that contributes to the overall benefit-risk evaluation that had not already been included in the CCDS at the beginning of the reporting interval.

The cumulative benefit, risk, and integrated benefit-risk evaluation sections of the most recently prepared PBRER should be reviewed and updated, if necessary.

2.7.3.2 Ad hoc (“for cause”) PBRERs

Ad hoc (“for cause”) PBRERs, i.e., reports outside the specified reporting requirements, are required by some regulatory authorities, generally when there are

new risks, when risks have changed, when efficacy/effectiveness has changed, or when there are changes to the benefit-risk profile of a medicinal product (see Section 3.17.1). Ad hoc PBRERs are not typically used to address urgent concerns. For all ad hoc PBRERs, it will be necessary for the regulatory authority to specify the duration of interval data.

It is likely that the appropriate data and evaluation sections will need to be updated, and focus on particular concerns raised in the ad hoc request. The overall benefit-risk evaluation and conclusion sections from the most recently submitted PBRER will need to be carefully reviewed and may require revision (Scenario D in Figure 1).

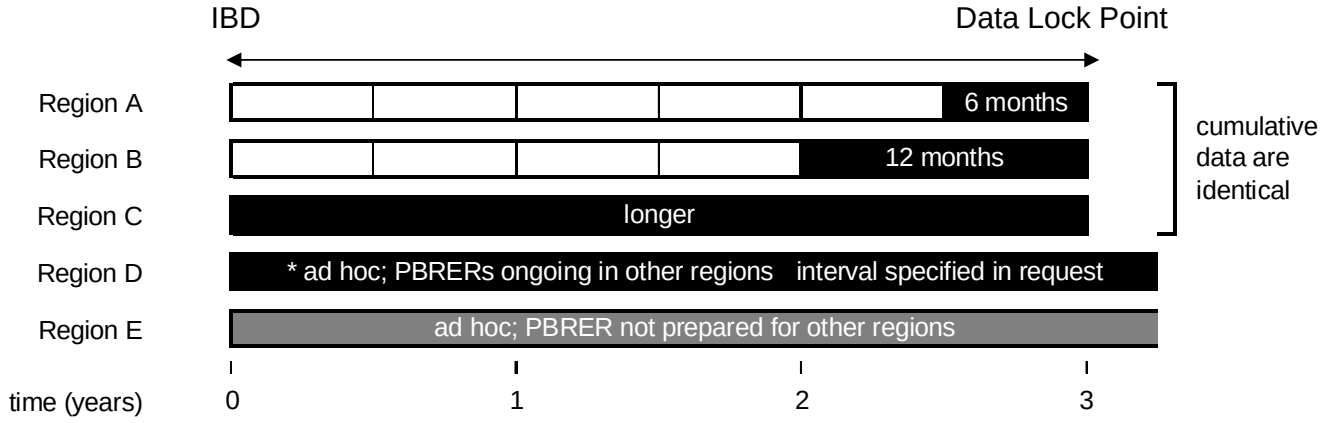
Where an ad hoc report is requested and a PBRER has not been prepared for a number of years, it is likely that a completely new report will need to be prepared by the MAH.

Where an ad hoc PBRER has been requested by one regulatory authority (e.g., in response to a new safety or benefit-risk concern), the MAH should consider communicating the findings at the same time to the regulatory authorities in other countries where the product is approved. Other regulatory authorities may request copies of the ad hoc PBRER, if desired.

Figure 1. Submission of PBRERs Based on the Same Data Lock Point, with Various Reporting Periods.

Shading indicates period of interval data.

For all reports, the cumulative data reflect all data from the IBD/DIBD.



* update the most recent cumulative and interval data, as appropriate

2.7.4 Time Interval between Data Lock Point and the Submission

As a result of the expanded scope of the PBRER, the time interval between the data lock point and submission of PBRERs should be as follows:

- PBRERs covering intervals of 6 or 12 months: within 70 calendar days
- PBRERs covering intervals in excess of 12 months: within 90 calendar days

- Ad hoc PBRERs: 90 calendar days, unless otherwise specified in the ad hoc request.

Where national or regional requirements differ from the above, the MAH should discuss the timeline for submission with the relevant regulatory authority.

2.8 Format and Presentation of PBRER

2.8.1 Format

The recommended format and content of the PBRER, including table of contents, section numbering, and content of each section, is outlined below.

The full ICH guideline E2C(R2) format should be used for all PBRERs. When no relevant information is available or a PBRER section is not applicable, this should be stated. In some countries and regions, the PBRER requirement may be linked to other regulatory documents for pre-approval periodic reporting (i.e., DSUR), post-marketing pharmacovigilance planning and/or risk management. The regulatory authorities and MAHs can take advantage of the modular approach of the PBRER (i.e., sections that can be separated and submitted independently or combined with other documents) to facilitate such regulatory needs, maximize the utility of the content, and reduce duplicate work.

2.8.2 Presentation

The recommended table of contents, including section numbering, for the PBRER is provided below:

Title Page

Executive Summary

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1. Introduction
2. Worldwide Marketing Approval Status
3. Actions Taken in the Reporting Interval for Safety Reasons
4. Changes to Reference Safety Information
5. Estimated Exposure and Use Patterns
    - 5.1 Cumulative Subject Exposure in Clinical Trials
    - 5.2 Cumulative and Interval Patient Exposure from Marketing Experience
6. Data in Summary Tabulations
    - 6.1 Reference Information
    - 6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials
    - 6.3 Cumulative and Interval Summary Tabulations from Post-marketing Data Sources
7. Summaries of Significant Findings from Clinical Trials during the Reporting Period
    - 7.1 Completed Clinical Trials

3 GUIDANCE ON CONTENTS OF THE PBRER

All sections should be completed; when no information is available, this should be stated. Note that section 3.X of this guideline provides information on preparation of Section X of the PBRER, i.e., "Reference Information," described in Section 3.6.1 of this guideline, refers to Section 6.1 of the PBRER.

Title Page

The title page of the PBRER should include the following information:

- date of the report;

- medicinal product(s);
- International Birth Date;
- reporting interval;
- MAH(s) name(s) and address(es); and
- statement on the confidentiality of the information included in the PBRER.

Executive Summary

This section should provide a concise summary of the most important information contained in the report.

The following information should be included in the Executive Summary:

- introduction;
- reporting interval;
- medicinal product(s) – mode(s) of action, therapeutic class(es), indication(s), dose(s), route(s) of administration, formulation(s);
- estimated cumulative exposure of clinical trial subjects; interval and cumulative post-approval exposure;
- number of countries in which the medicinal product is approved;
- summary of overall benefit-risk evaluation (based on Section 18.2 of the PBRER);
- actions taken or proposed for safety reasons, e.g., significant changes to the labelling, other risk minimisation activities;
- conclusions.

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3.1 Introduction

Section 1 of the PBRER should include:

- international birth date;
- reporting interval;
- medicinal product(s) – mode(s) of action, therapeutic class(es), dose(s), route(s) of administration, formulation(s);
- a brief description of the approved indication(s) and population(s)
- a brief description and explanation of any information that has not been included in the PBRER; and
- the rationale for submission of multiple PBRERs for the medicinal product, if applicable.

3.2 Worldwide Marketing Approval Status

Section 2 of the PBRER should provide a brief narrative overview including date of first approval, indication(s), approved dose(s), and where approved, if applicable.

3.3 Actions Taken in the Reporting Interval for Safety Reasons

Section 3 of the PBRER should include a description of significant actions related to safety that have been taken during the reporting interval, related to either investigational uses or marketing experience, by the MAH, sponsor of a clinical trial(s), regulatory authorities, data monitoring committees, or ethics committees that had:

- a significant influence on the benefit-risk profile of the approved medicinal product, and/or
- an impact on the conduct of a specific clinical trial(s) or on the overall clinical development programme.

The reason(s) for each action should be provided, if known, and additional relevant information should be provided when appropriate. Relevant updates to previous actions should also be summarised in this section. Examples of significant actions taken for safety reasons include:

Actions related to investigational drugs:*

- refusal to authorise a clinical trial for ethical or safety reasons;
- partial[5] or complete clinical trial suspension or early termination of an ongoing clinical trial* because of safety findings or lack of efficacy;
- recall of investigational drug or comparator;
- failure to obtain marketing approval for a tested indication, including voluntary withdrawal of a marketing application;
- risk management activities, including:
    - protocol modifications due to safety or efficacy concerns (e.g., dosage changes, changes in study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration);
    - restrictions in study population or indications;
    - changes to the informed consent document relating to safety concerns;
    - formulation changes;
    - addition by regulators of a special safety-related reporting requirement;
    - issuance of a communication to investigators or healthcare professionals; and
    - plans for new studies to address safety concerns.

Actions related to marketed drugs:

- failure to obtain a marketing approval renewal;
- withdrawal or suspension of a marketing approval;
- risk management activities including:

[5] "Partial suspension" might include several actions (e.g., suspension of repeat dose studies, but continuation of single dose studies; suspension of trials in one indication, but continuation in another, and/or suspension of a particular dosing regimen in a trial but continuation of other doses).

- o Significant restrictions on distribution or introduction of other risk minimisation measures;
- o significant safety-related changes in labelling documents that could affect the development programme, including restrictions on use or population treated;
- o communications to health care professionals; and
- o new post-marketing study requirement(s) imposed by regulators.

3.4 Changes to Reference Safety Information

Section 4 of the PBRER should list any significant changes to the reference safety information within the reporting interval. Such changes might include information relating to contraindications, warnings, precautions, serious adverse drug reactions (ADRs), adverse events of special interest, and interactions; important findings from ongoing and completed clinical trials;* and significant non-clinical findings (e.g., carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the PBRER. A tracked changes version of the reference document should be included (as an attachment) that identifies changes over the reporting interval.

The MAH should also provide, in a regional appendix, information on any final, ongoing, or proposed changes to the national or local authorised product information based on the most recent version of the CCSI.

3.5 Estimated Exposure and Use Patterns

Sections 5.1 and 5.2 of the PBRER should provide estimates of the size and nature of the population exposed to the medicinal product. Section 5.1 of the PBRER should provide information on cumulative exposure in clinical trials. Section 5.2 should provide cumulative and interval exposure in the marketed setting. Brief descriptions of the method(s) used to estimate the subject/patient exposure should be described, as well as the limitations thereof. Consistent methods for calculating patient exposure should be used across PBRERs for the same product. If a change in the method is appropriate, both methods and calculations should be provided in the PBRER introducing the change.

3.5.1 Cumulative Subject Exposure in Clinical Trials

Section 5.1 of the PBRER should include the following information, if applicable, presented in tabular format (see Appendix B, Tables 1-3 for examples):

- Cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational medicinal product, placebo, and/or active comparator(s) since the DIBD. It is recognised that for older products, detailed data might not be available.
- More detailed cumulative subject exposure in clinical trials should be presented if available, e.g., sub-grouped by age, sex, and racial group for the entire development programme.
- Important differences among trials in dose, routes of administration, or patient populations can be noted in the tables, if applicable, or separate tables can be considered.

- If clinical trials have been or are being performed in special populations (e.g., pregnant women; patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic polymorphisms), exposure data should be provided, as appropriate.
- When there are substantial differences in time of exposure between subjects randomised to the investigational medicinal product or comparator(s), or disparities in length of exposure between clinical trials, it can be useful to express exposure in subject-time (subject-days, -months, or -years).
- Investigational drug exposure in healthy volunteers might be less relevant to the overall safety profile, depending on the type of adverse reaction, particularly when subjects are exposed to a single dose. Such data can be presented separately with an explanation as appropriate.
- If the serious adverse events (SAEs) from clinical trials are presented by indication in the summary tabulations, the patient exposure should also be presented by indication, where available.
- For individual trials of particular importance, demographic characteristics should be provided separately.

3.5.2 Cumulative and Interval Patient Exposure from Marketing Experience

When possible, separate estimations should be provided for cumulative exposure (since the IBD) and interval exposure (since the data lock point of the previous PBRER), see Appendix B, Tables 4-5 for examples. Although the difficulty of obtaining and validating exposure data is recognised, the estimated number of patients exposed should be provided when possible, along with the method(s) used to determine the estimate. A justification should be provided if an estimate of the number of patients exposed is impossible to obtain. If an estimate of the number of patients is not available, alternative estimated measures of exposure, if available, should be presented along with the method(s) used to derive them. Examples of alternative measures of exposure include patient-days of exposure and number of prescriptions. Only if such measures are not available, measures of drug sales, such as tonnage or dosage units, may be used. The concept of a defined daily dose may also be used to arrive at patient exposure estimates.

The data should be presented according to the following categories:

1. Post-approval (non-clinical trial) exposure:

An overall estimation of patient exposure should be provided.

In addition, the data should be routinely presented by indication, sex, age, dose, formulation, and region, where applicable.

Depending upon the product, other variables may be relevant, such as number of vaccination courses, route(s) of administration, and duration of treatment.

When there are patterns of reports indicating a safety signal, exposure data within relevant subgroups should be presented, if possible.

2. Post-approval use in special populations

Where post-approval use has occurred in special populations, available information regarding cumulative patient numbers exposed and the method of calculation should

be provided. Sources of such data would include non-interventional studies designed to obtain this information, including registries. Populations to be considered for discussion include, but might not be limited to:

- paediatric population;
- elderly population;
- pregnant or lactating women;
- patients with hepatic and/or renal impairment;
- patients with other relevant co-morbidity;
- patients with disease severity different from that studied in clinical trials;
- sub-populations carrying relevant genetic polymorphism(s);
- patients of different racial and/or ethnic origins.

3. Patterns of Use of the Medicinal Product

If the MAH becomes aware of patterns of use of the medicinal product considered relevant for the interpretation of safety data, provide a brief description thereof. Such patterns may include, in particular, off-label use (e.g., an anti-epileptic drug used off-label for neuropathic pain and/or prophylaxis of migraine headaches). If known, the MAH may briefly comment on whether such off-label use is supported by clinical guidelines, clinical trial evidence, or an absence of approved alternative treatments. Quantitative use information should be provided, if available. For purposes of identifying which patterns of use are off-label, the MAH should reference the CCDS in the PBRER.

3.6 Data in Summary Tabulations

Sections 6.1-6.3 of the PBRER should present cumulative summary tabulations of SAEs from clinical trials and post-marketing sources that have been reported to the MAH since the DIBD. At the discretion of the MAH, graphical displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

3.6.1 Reference Information

Section 6.1 of the PBRER should specify the version(s) of the coding dictionary used for analyses of adverse reactions.

3.6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

Section 6.2 of the PBRER should provide background for the appendix that provides a cumulative summary tabulation of SAEs reported in the MAH's clinical trials, from the DIBD to the data lock point of the current PBRER. The MAH should explain any omission of data (e.g., clinical trial data might not be available for products marketed for many years). The tabulation(s) should be organised by system organ class (SOC), for the investigational drug, as well as for the comparator arm(s) (active comparators, placebo) used in the clinical development programme. Data can be integrated across the programme. Alternatively, when useful and feasible, tabulations of SAEs can be presented by trial, indication, route of administration, or

other variables. This section should not serve to provide analyses or conclusions based on the SAEs.

Appendix B, Table 6 of this guideline provides an example of summary tabulations of serious adverse events from clinical trials. The following points should be considered:

- In general, the tabulation(s) of SAEs from clinical trials should include only those terms that were used in defining the case as serious; they should not include non-serious events.
- When the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the Preferred Term level and SOC should be presented in the summary tabulations.
- The tabulations should include blinded and unblinded clinical trial data. Unblinded serious adverse events might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g., expedited reporting), if applicable. Sponsors/MAHs should not unblind data for the specific purpose of preparing the PBRER.
- Certain adverse events in clinical trials can be excluded from the clinical trials summary tabulations, but such exclusions should be explained in the report. For example, adverse events that have been defined in the protocol as "exempt" from special collection and entry into the safety database because they are anticipated in the patient population, and those that represent study endpoints, can be excluded (e.g., deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).
- Causality assessment is generally useful for the evaluation of individual rare ADRs. Individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. Therefore, the summary tabulations should include all SAEs for the investigational drug, active controls, and placebo. It may be useful to give rates by dose.

3.6.3 Cumulative and Interval Summary Tabulations from Post-marketing Data Sources

Section 6.3 of the PBRER should provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the data lock point of the current PBRER. These adverse reactions are derived from non-interventional studies and spontaneous ICSRs, including reports from healthcare professionals, consumers, scientific literature, regulatory authorities. Serious and non-serious reactions should be presented in a single table, with interval and cumulative data presented side-by-side (see Appendix B, Table 7). The table should be organised by SOC. For special issues or concerns, additional tabulations of adverse reactions can be presented by indication, route of administration, or other variables. This section should not serve to provide analyses or conclusions based on the data presented. As described in ICH guideline E2D, for marketed medicinal products, spontaneously reported* adverse events usually imply at least a suspicion of causality by the reporter, and should be considered to be adverse reactions for regulatory reporting purposes.

3.7 Summaries of Significant Safety Findings from Clinical Trials during the Reporting Period

A listing of any MAH-sponsored interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk management measures that were completed or ongoing during the reporting interval (i.e., post-authorisation safety studies, PASS*), should be included in an appendix.

When possible and relevant, data categorized by sex and age (particularly children versus adult), indication, dose, and region should be presented.

The signals arising from clinical trial sources should be tabulated in Section 15 of the PBRER. For those that are considered to be either a potential* or identified risk,* the risk should be evaluated and characterised in Sections 16.3 and 16.4, respectively.

3.7.1 Completed Clinical Trials

Section 7.1 of the PBRER should provide a brief summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting interval. This information can be presented in narrative format or as a synopsis. It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

3.7.2 Ongoing Clinical Trials

If the MAH is aware of clinically important information that has arisen from ongoing clinical trials (e.g., learned through interim safety analyses or as a result of unblinding of subjects with adverse events), this section should briefly summarise the concern(s). It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

3.7.3 Long-term Follow-up

Where applicable, this section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products.

3.7.4 Other Therapeutic Use of Medicinal Product

This section of the PBRER should include clinically important safety information from other programmes conducted by the MAH that follow a specific protocol, with solicited reporting as per ICH guideline E2D (e.g., expanded access programmes, compassionate use programmes, particular patient use, single-patient investigational new drug applications (INDs), treatment INDs, and other organised data collection).

3.7.5 New Safety Data Related to Fixed Combination Therapies

Unless otherwise specified by national or regional regulatory requirements, the following options can be used to present data from combination therapies.

- If the product that is the subject of a PBRER is also approved or under development as a component of a fixed combination product or a multi-drug regimen, this section should summarise important safety findings from use of the combination therapy.

- If this PBRER is for a fixed combination product, this section should summarise important safety information arising from the individual components whether approved or under development.

The information specific to the combination can be incorporated into a separate section(s) of the PBRER for one or all of the individual components of the combination.

3.8 Findings from Non-interventional Studies

This section should summarise relevant safety information or information with potential impact on the benefit or risk evaluations, from MAH-sponsored non-interventional studies that became available during the reporting interval (e.g., observational studies, epidemiological studies, registries, and active surveillance programmes). This should include relevant information from drug utilisation studies when applicable to multiple regions.

A listing of any MAH-sponsored non-interventional study(s) with the primary aim of identifying, characterising, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk management measures that were completed or ongoing during the reporting interval (i.e., post-authorisation safety studies), should be included in an appendix. Progress or final study reports generated during the reporting period for post-authorisation safety studies (PASS) should also be included as a regional appendix to the report.

3.9 Information from Other Clinical Trials and Sources

This section should summarise information relevant to the risk evaluation of the medicinal product from any other clinical trial/study sources that is accessible by the MAH with reasonable and appropriate effort, and became available to the MAH during the reporting interval (e.g., results from pooled analyses or meta-analyses of randomised clinical trials, safety information provided by co-development partners or from investigator-initiated trials).

3.10 Non-clinical Data

This section should summarise major safety findings from non-clinical *in vivo* and *in vitro* studies (e.g., carcinogenicity, reproduction, or immunotoxicity studies) ongoing or completed during the reporting interval. Implications of these findings should be discussed in Sections 16 and 18 of the PBRER.

3.11 Literature

This section should summarise new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts, relevant to the approved medicinal product that the MAH became aware of during the reporting interval. Literature searches for PBRERs should be wider than those for individual adverse reaction cases as they should also include studies reporting safety outcomes in groups of subjects. If relevant and applicable, information on active substances of the same class should be considered.

3.12 Other Periodic Reports

Unless otherwise specified by national or regional regulatory requirements, the MAH should prepare a single PBRER for a single active substance. However, if an MAH prepares multiple PBRERs for a single medicinal product (e.g., covering different

indications, or formulations), this section should summarise significant findings from the other periodic reports if they are not presented elsewhere within this report.

When available, based on contractual agreements, the MAH should summarise significant findings from periodic reports provided during the reporting interval by other parties (e.g., sponsors, MAHs, other contractual partners).

3.13 Lack of Efficacy in Controlled Clinical Trials

Data from clinical trials indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for products intended to treat or prevent serious or life-threatening illnesses (e.g., excess cardiovascular adverse events in a trial of a new anti-platelet drug for acute coronary syndromes) could reflect a significant risk to the treated population and should be summarised in this section. When relevant to the benefit-risk evaluation, clinical trials demonstrating lack of efficacy for products not intended for treatment of life-threatening diseases in the approved indications should also be summarised.

3.14 Late-Breaking Information

This section should summarise information on potentially important safety and efficacy/effectiveness findings that arise after the data lock point, but while the PBRER is in preparation. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the MAH, a data monitoring committee, or a regulatory authority has taken for safety reasons. New individual case reports should not be included unless they are considered to constitute an important index case (i.e., the first instance of an important event) or an important safety signal.

The Evaluation of Risks and New Information (see Section 3.16.3 of this guideline) should also take these new data into account.

3.15 Overview of Signals: New, Ongoing, or Closed

The purpose of this section is to provide an overview of signals detected, under review, and evaluated during the reporting interval.

A brief description of the method of signal detection* used, as well as the sources screened for signals, should be provided.

A newly identified signal refers to a signal that has been identified during the reporting interval. An ongoing signal refers to a signal that was still under evaluation at the data lock point. A closed signal refers to a signal for which an evaluation was completed during the reporting interval. Signals that are both newly identified and closed during the reporting interval should be handled in this section as closed signals (i.e., signals detected during the reporting period, with evaluation completed within the reporting period).

This section should reference a tabulation of signals that are new, ongoing, and closed during the reporting interval. The tabulation should be provided as an appendix to the PBRER and conform to the template annexed to this guideline (see Appendix C). At the discretion of the MAH, this tabulation may also provide cumulative signal data by including previously closed signals, in which case the MAH should specify the starting point (date) for the cumulative data.

Detailed signal evaluations will not be included in this section but will instead be presented in Sections 16.2 (Signal Evaluation) and 16.3 (Evaluation of Risks and New Information) of the PBRER.

3.16 Signal and Risk Evaluation

3.16.1 Summary of Safety Concerns

The purpose of this section is to provide a summary of important safety concerns at baseline, i.e., at the beginning of the reporting interval, against which new information and evaluations can be made. The following factors should be considered when determining the importance of each risk:

- medical seriousness of the risk, including the impact on individual patient;
- its frequency, predictability, preventability, and reversibility;
- potential impact on public health (frequency; size of treated population); and
- public perception of risk where it may impact public heath, e.g., avoidance of vaccines.

The summary should present the following safety information, as of the beginning of the reporting interval of the current PBRER:

- important identified risks;*
- important potential risks;* and
- important missing information.*

For products with an existing safety specification, this will be the same as the safety specification summary of ICH guideline E2E at the start of the reporting interval.

For products without an existing safety specification, this section should provide information on the important identified and potential risks associated with use of the product, based on pre- and post-approval experience. These may include, for example:

- important adverse reactions;
- interactions with other medicinal products;
- interactions with foods and other substances;
- medication errors;
- effects of occupational exposure; and
- pharmacological class effects.

The summary on important missing information should take into account whether there are critical gaps in knowledge for specific safety issues or populations that use the medicinal product.

3.16.2 Signal Evaluation

Section 16.2 of the PBRER should summarize the results of evaluations of safety signals that were closed during the reporting interval. There will be two main categories:

1. Those signals that, following evaluation, have been categorised as a potential or identified risk, including lack of efficacy. These closed signals should be discussed in PBRER Section 16.3, Evaluation of Risks and New Information.

2. Those signals that, following evaluation, have been rejected as false signals based on a scientific evaluation of the currently available information. For this category of signals, a description of each signal evaluation should be included in order to provide the basis upon which the signal was rejected. This description can be included in this section of the PBRER, or in an appendix.

For signals that have had a completed evaluation during the interval, it is recommended that the level of detail provided in the description of the signal evaluation be proportionate to the public health importance of the concern and the extent of the available evidence, and should include the following information as appropriate:

- source or trigger of the signal;
- background relevant to the evaluation;
- methods of evaluation, including data sources, search criteria, and analytical approaches;
- results – a summary and critical analysis of the data considered in the signal evaluation;
- discussion; and
- conclusion, including proposed actions.

3.16.3 Evaluation of Risks and New Information

This section should provide a critical appraisal of all new information on all risks, which can be categorised as “important” or “other.” This includes newly detected potential and identified risks, as well as new information relevant to previously identified risks. This section should not summarise or repeat information presented in previous sections of the PBRER, but should provide an interpretation of the new information, with a view towards characterising the risk profile.

New information can be organised as follows:

1. new potential risks
2. new identified risks
3. new information on previously detected risks (potential or identified)
4. update on important missing information

Concise summaries of the evaluations of important risks should be provided. For “other” risks not classified as “important,” for which new information has emerged during the reporting interval, the level of detail should be proportional to the available evidence on the risk and its public health relevance.

Any new information on populations exposed or data generated to address previously missing information should be critically assessed in this section. Unresolved concerns and uncertainties should be acknowledged.

3.16.4 Characterisation of Risks

This section will characterise important identified and potential risks based on cumulative data (i.e., not restricted to the reporting interval), and describe important missing information.

Depending on the nature of the data source, the characterisation of risk may include, where applicable:

- frequency;
- numbers of cases (numerator); precision of estimate, taking into account the source of the data;
- extent of use (denominator) expressed as numbers of patients, patient-time, etc., and precision of estimate;
- estimate of relative risk; precision of estimate;
- estimate of absolute risk; precision of estimate;
- impact on the individual patient (effects on symptoms, quality or quantity of life);
- public health impact;
- risk factors (e.g., patient factors [age, pregnancy/lactation, hepatic/renal impairment, relevant co-morbidity, disease severity, genetic polymorphism, racial and/or ethnic origin], dose);
- duration of treatment, risk period;
- preventability (i.e., predictability, ability to monitor for a “sentinel” adverse reaction or laboratory marker);
- reversibility;
- potential mechanism; and
- strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable.

For PBRERs for products with several indications, formulations, or routes of administration, where there may be significant differences in the identified and potential risks, it may be appropriate to present risks by indication, formulation, or route of administration. Headings that could be considered include:

- risks relating to the active substance;
- risks related to a specific formulation or route of administration (including occupational exposure);
- risks relating to a specific population;
- risks associated with non-prescription use (for compounds that are available as both prescription and non-prescription products); and
- safety concerns regarding missing information.

3.16.5 Effectiveness of Risk Minimisation (if applicable)

Relevant information on the effectiveness and/or limitations of specific risk minimisation activities for important identified risks that has become available during the reporting interval should be summarised in this section.

Insights into the effectiveness of risk minimisation activities that may be applicable across multiple regions are of particular interest. Information may be summarised by region, if applicable and relevant.

Results of evaluations that became available during the reporting interval should be provided in regional appendices to comply with national or regional requirements.

3.17 Benefit Evaluation

3.17.1 Important Baseline Efficacy/Effectiveness Information

This section summarises information on the efficacy/effectiveness of the medicinal product at baseline, i.e., as of the beginning of the reporting interval. This information should relate to the approved indication(s) of the medicinal product, listed in the CCDS.

For medicinal products with multiple indications, populations, and/or routes of administration, the benefit should be characterised separately by these factors.

When there have been no significant changes in the benefit or risk profile of the medicinal product in the reporting interval, the summary should be succinct, essentially the content of the CCDS.

For medicinal products where there have been significant changes in either the risk or benefit profile, the section should include sufficient information to support an updated characterisation of the benefit of the medicinal product in section 17.3 of the PBRER. The type and extent of the information presented will vary by product, and may include the following, if available and relevant:

- a brief description of the epidemiology and natural history of the disease;
- nature of the benefit: e.g., diagnostic, preventive, symptomatic, or disease-modifying treatment;
- important endpoints that support the benefit, e.g., effects on mortality, symptoms, patient reported outcomes;
- evidence of efficacy/effectiveness of comparators, e.g., active-controlled trials, meta-analyses, observational studies, if applicable; and
- when relevant to the benefit-risk evaluation, trends, patterns and/or evidence of benefit in important subgroups, e.g., age, sex, ethnicity, disease severity, or genetic polymorphism.

3.17.2 Newly Identified information on Efficacy/Effectiveness

Additional information on efficacy/effectiveness in approved indications that may have become available during the reporting interval should be presented in this section. For approved indications, new information on efficacy/effectiveness under conditions of actual use should also be described in this section, if available. New information about efficacy/effectiveness in uses other than the approved indication(s)

should not be included, unless relevant for the benefit-risk evaluation in the approved indication.

Particular attention should be given to changes in the therapeutic environment that could impact efficacy/effectiveness over time, e.g., vaccines, emergence of resistance to anti-infective agents, availability of new medicinal products.

The type and extent of the information presented will vary by product, and could refer to PBRER section 17.1 if no new information became available.

3.17.3 Characterisation of Benefits

Section 17.3 of the PBRER provides an integration of the baseline benefit information and any relevant new benefit information that became available during the reporting interval for approved indications.

When there are no new relevant benefit data, and no significant change in risk profile, this section should refer to PBRER Section 17.1.

When there is new positive benefit information and no significant change in the risk profile in this reporting interval, the integration of baseline and new information in this section should be succinct.

When there is significant change to the risk profile, or new evidence that suggests benefit is significantly less than originally demonstrated, this section should provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy/effectiveness, considering the following, when available:

- a brief description of the strength of evidence of benefit, considering comparator(s), effect size, statistical rigor, methodological strengths and deficiencies, and consistency of findings across trials/studies;
- new information that challenges the validity of a surrogate endpoint, if used;
- clinical relevance of the effect size;
- generalizability of treatment response across the indicated patient population, e.g., information that demonstrates lack of treatment effect in a sub-population;
- adequacy of characterization of dose-response;
- duration of effect;
- comparative efficacy; and
- a determination of the extent to which efficacy findings from clinical trials are generalizable to patient populations treated in medical practice.

3.18 Integrated Benefit-risk Analysis for Approved Indications

The purpose of this section is to provide an overall appraisal of the benefit and risk of the medicinal product as used in clinical practice. This section should provide a critical analysis and integration of the information in the previous sections with respect to benefit and risk, and should not duplicate the benefit and risk information presented in Sections 16.3 and 17.3.

3.18.1 Benefit-risk Context - Medical Need and Important Alternatives

This section should provide a brief description of the medical need for the medicinal product in the approved indications, and summarise alternatives (medical, surgical, or other; including no treatment).

3.18.2 Benefit-risk Analysis Evaluation

A benefit-risk profile is specific to an indication and population. For products approved for more than one indication, benefit-risk profiles should be evaluated and presented for each indication individually. If there are important differences in the benefit-risk profiles among populations within an indication, benefit-risk evaluation should be presented by population, if possible. The benefit-risk evaluation should be presented in a structured manner as described below.

General points regarding benefit and risk:

- Whereas previous sections will include all important benefit and risk information, not all benefits and risks contribute importantly to the overall benefit-risk evaluation. Therefore, the key benefits and risks considered in the evaluation should be specified. The key information presented in the previous benefit and risk sections should be carried forward for integration in the benefit-risk evaluation.
- Consider the context of use of the medicinal product: the condition to be treated, prevented, or diagnosed; its severity and seriousness; and the population to be treated (relatively healthy; chronic illness).
- With respect to benefit, consider its nature, clinical importance, duration, and generalizability, as well as evidence of efficacy in non-responders to other therapies and alternative treatments. Consider the effect size. If there are individual elements of benefit, consider all (e.g., for therapies for arthritis: reduction of symptoms and inhibition of radiographic progression of joint damage).
- With respect to risk, consider its clinical importance, e.g., nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients, and whether it arose from off-label use, a new use, or misuse.
- The strengths, weaknesses, and uncertainties of the evidence should be considered when formulating the benefit-risk evaluation. Describe how uncertainties in the benefits and risks impact the evaluation. For example, uncertainty in important benefits and/or risks may reduce their contribution(s) to the evaluation. Limitations of the assessment should be discussed.

Provide a clear explanation of the methodology and reasoning used to develop the benefit-risk evaluation:

- The assumptions, considerations, and judgement or weighting that support the conclusions of the benefit-risk evaluation should be clear.
- Comment on the feasibility of expressing benefits and risks in such a way as to facilitate their comparison.
- If a formal quantitative assessment of benefit-risk is provided, a summary of the methods should be included.

- Economic considerations (e.g., cost-effectiveness) should not be considered in the benefit-risk evaluation.

When there is important new information or an ad hoc PBRER has been requested, a detailed benefit-risk analysis based on cumulative data would be appropriate. Conversely, where little new information has become available during the reporting interval, the primary focus of the benefit-risk evaluation might consist of an evaluation of updated interval safety data, with the understanding that the overall benefit-risk profile has not changed during the reporting interval.

3.19 Conclusions and Actions

This section should provide a conclusion about the implications of any new information that arose during the reporting interval, in terms of the overall benefit-risk evaluation, for each approved indication, as well as for relevant subgroups, if appropriate.

Based on the evaluation of the cumulative safety data and the benefit-risk analysis, the MAH should assess the need for changes to the CCDS and propose changes as appropriate.

In addition, the conclusion should include preliminary proposal(s) to optimise or further evaluate the benefit-risk balance, for further discussion with the relevant regulatory authorities. This may include proposals for additional risk minimisation activities.

For products with an E2E (Pharmacovigilance Planning) document, the proposals should be incorporated into the E2E pharmacovigilance plan and risk minimisation plan.

3.20 Appendices to the PBRER

The PBRER should be accompanied by the following appendices, as appropriate, numbered as follows:

1 Reference Information;

2 Cumulative Summary Tabulation of Serious Adverse Events from Clinical trials and Interval/Cumulative Summary Tabulations from Marketed Experience;

3 Tabular Summary of Safety Signals;

4 Listing of all Post-authorisation Safety Studies (PASS);

5 List of the Sources of Information Used to Prepare the PBRER (when desired by the MAH).

The PBRER may also be accompanied by regional appendices, as needed, to fulfil national and regional requirements.

4 APPENDICES TO THIS GUIDELINE

Appendix A Glossary

Appendix B Examples of Summary Tabulations

Appendix C Tabular Summary of Safety Signals that were New, Ongoing, or Closed during the Reporting Interval

Appendix D List of PBRER Sections, Identified as Providing Cumulative or Interval Information, and Ability to Share Modules with Other Regulatory Documents

Appendix E Examples of Possible Sources of Information That May Be Used in the Preparation of the PBRER[6]

[6] Examples of potential sources of information to be used in preparation of a PBRER will be included in the Step 4 guideline as general guidance. Suggestions for information sources to be included in this list should be submitted during the consultation period.

APPENDIX A – Glossary

Whenever possible the Working Group has used terms in use in other ICH guidelines, or those previously proposed by Council for International Organizations of Medical Sciences (CIOMS) working groups. Generally, the definitions of terms previously defined in ICH documents are not repeated in this glossary, except for those of particular importance to the PBRER.

Item	Glossary Term	Source of Definition	Definition/Commentary
1.	Closed signal	ICH guideline E2C (R2)	A signal for which an evaluation was completed during the reporting interval.
2.	Company Core Data Sheet (CCDS)	ICH guideline E2C	A document prepared by the MAH containing, in addition to safety information, material related to indications, dosing, pharmacology and other information concerning the product.
3.	Company Core Safety Information (CCSI)	ICH guideline E2C	All relevant safety information contained in the CCDS prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purposes of periodic reporting for marketed products, but not by which expected ad unexpected are determined for expedited reporting.
4.	Completed clinical trial	ICH guideline E2F	Study for which a final clinical study report is available.
5.	Identified risk	ICH guideline E2F	An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Examples of identified risks include: • an adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data; • an adverse reaction observed in well designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group (placebo or active substance) on a parameter of interest suggests a causal relationship;

Item	Glossary Term	Source of Definition	Definition/Commentary
			• an adverse reaction suggested by a number of well documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.
6.	Important identified risk, important potential risk	ICH guideline E2C(R2)	An identified risk or potential risk that could impact on the risk-benefit profile of the product or have implications for public health. What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk, and the impact on public health. Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product labelling should be considered important.
7.	Important missing information	ICH guideline E2C(R2)	Critical gaps in knowledge for specific safety issues or populations that use the marketed product.
8.	Investigational drug	ICH guideline E2F	The term investigational drug is used in this guideline to indicate only the experimental product under study or development. Note: This term is more specific than "investigational medicinal product", which includes comparators and placebos.
9.	Module/modular approach	ICH guideline E2C(R2)	Sections of a report that have been written to facilitate their use in more than one regulatory document.
10.	Newly identified signal	ICH guideline E2C(R2)	A signal first identified during the reporting interval, prompting further actions for evaluation.
11.	Non-interventional clinical study	ICH guideline E2F	A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing approval. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the

Item	Glossary Term	Source of Definition	Definition/Commentary
			patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.
12.	Ongoing clinical trial	ICH guideline E2F	Trial where enrolment has begun, whether a hold is in place or analysis is complete, but for which a final clinical study report is not available.
13.	Ongoing signal	ICH guideline E2C (R2)	A signal that had been identified before the reporting interval, that was still under evaluation at the data lock point.
14.	Post-Authorisation Safety Study (PASS)	Revised 2001/83/EC amendment (Article 1[c] 15)	Any study relating to an approved medicinal product conducted with the aim of identifying, characterising, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.
15.	Potential risk	ICH guideline E2F	An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. Examples of potential risks include: • non-clinical safety concerns that have not been observed or resolved in clinical studies; • adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on the parameter of interest raises a suspicion of, but is not large enough to suggest, a causal relationship; • a signal arising from a spontaneous adverse reaction reporting system; • an event which is known to be associated with other products of the same class or which could be expected to occur based on the properties of the

Item	Glossary Term	Source of Definition	Definition/Commentary
			medicinal product.
16.	Reference Safety Information	ICH guideline E2C(R2)	Referred to as the CCSI, a subset of information contained within the MAH's central document (CCDS).
17.	Risk minimisation activities	ICH guideline E2C(R2)	Public health interventions intended to prevent or reduce the probability of the occurrence of ADRs associated with the exposure to a medicine, or to reduce their severity should they occur. The aim of a risk minimisation activity is to reduce the probability or severity of an adverse reaction. These activities may consist of routine risk minimisation (e.g., product labelling) or additional risk minimisation activities (e.g., professional or patient communications/educational materials).
18.	Safety concern	ICH guideline E2C(R2)	An important identified risk, important potential risk, or important missing information.
19.	Signal	ICH guideline E2C(R2)	Information that arises from one or multiple sources (including observations and experiments), that suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify further action to verify.
20.	Signal detection	ICH guideline E2C(R2)	The act of looking for and/or identifying signals using data from any source. It should be noted that a safety signal is not synonymous with a statistic of disproportionate reporting, a numerical result above a preset threshold generated from any data mining algorithm using disproportionality analysis applied to a spontaneous report database.
21.	Spontaneous Report or Spontaneous Notification	ICH guideline E2D	An unsolicited communication to a company, regulatory authority, or other organization that describes an ADR in a patient given one or more medicinal products and which does not derive from a study or any organized data collection

Item	Glossary Term	Source of Definition	Definition/Commentary
			scheme.

APPENDIX B – Examples of Summary Tabulations

Table 1 – Estimated Cumulative Subject Exposure from Clinical Trials

Estimates of cumulative subject exposure, based upon actual exposure data from completed clinical trials and the enrolment/randomisation schemes for ongoing trials.

Treatment	Number of subjects
medicinal product	
Comparator	
Placebo	

Table 2 – Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by Age and Sex*

	Number of subjects		
Age range	Male	Female	Total

* Data from completed trials as of [date]

Table 3 – Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by Racial Group*

Racial group	Number of subjects
Asian	
Black	
Caucasian	
Other	
Unknown	
Total	

* Data from completed studies as of [date]

Table 4 – Cumulative Exposure from Marketing Experience

indication	sex		age (years)				dose (mg/day)			formulation		region				
	male	female	2 to ≤16	>16 to 65	>65	unknown	<40	≥40	unknown	IV	oral	EU	Japan	Mexico	US/Canada	other
depression																
migraine																

Table 4 includes cumulative data obtained from month/day/year through month/day/year, where available.

Table 5 – Interval Exposure from Marketing Experience

indication	sex		age (years)				dose (mg/day)			formulation		region				
	male	female	2 to ≤16	>16 to 65	>65	unknown	<40	≥40	unknown	IV	oral	EU	Japan	Mexico	US/Canada	other
depression																
migraine																

Table 5 includes interval data obtained from month/day/year through month/day/year, where available.

Table 6 – Cumulative Tabulations of Serious Adverse Events from Clinical Trials

System Organ Class Preferred Term	[medicinal product]	Blinded	Active comparator	Placebo
Investigations	n	n	n	n
Alanine aminotransferase increased	n	n	n	n
Aspartate aminotransferase increased	n	n	n	n
Nervous System Disorders	n	n	n	n
Syncope	n	n	n	n
Headache	n	n	n	n

Table 7 - Numbers of Adverse Drug Reactions by Term from Post-marketing Sources*

	Spontaneous, including regulatory authority and literature				Non-interventional post-marketing study				Total
	serious		non-serious		serious		non-serious**		
	interval	cumulative	interval	cumulative	interval	cumulative	interval	cumulative	cumulative, all
SOC 1									
MedDRA PT									
MedDRA PT									
MedDRA PT									
SOC 2									
MedDRA PT									
MedDRA PT									
MedDRA PT									
MedDRA PT									

*Non-interventional studies and spontaneous ICSRs (i.e., reports from healthcare professionals, consumers, regulatory authorities, and scientific literature)

** Non-serious ADRs from non-interventional Post-Authorisation Safety Studies (PASS) only should be tabulated here. See Glossary.

APPENDIX C – Tabular Summary of Safety Signals that were New, Ongoing, or Closed during the Reporting Interval

Product Name: _____

Reporting Interval: DD-MMM-YYYY to DD-MMM-YYYY

Signal term	Date detected	Status (new, ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
stroke	month/year	new	month/year	spontaneous, animal	brief summary of key data and rationale for further evaluation	review cases; epidemiological studies	

Explanatory notes

- Signal term

  A brief descriptive name of a medical concept for the signal. This may evolve and be refined as the signal is evaluated. The concept and scope may or may not be limited to specific MedDRA term(s), depending on the source of signal. Where applicable, the table should refer to the specific MedDRA terms (e.g., PTs, HLTs, SOCs, etc.) or Standardised MedDRA Queries (SMQs) that were reviewed.

- Date detected (month/year)

  Month and year when the signal was detected (that is, when a determination was made to conduct further evaluation).

- Status

  New: Signal identified during the reporting interval.

  Ongoing: Signal under evaluation at the data lock point (the end of the reporting interval). Provide anticipated completion date, if known.

  Closed: Signal for which evaluation was completed during the reporting interval.

  Note: A signal may be “new” and “closed” if an evaluation of a newly identified signal was completed within the reporting interval. The signal should be identified as “new and closed” in the tabulation, but handled as a closed signal for the purposes of the evaluation (see Section 3.16.2 of this guideline).

- Date closed (month/year)

Month and year when the signal evaluation was completed.

- Source or trigger of signal

  Data or information source from which a signal arose. Examples include, but may not be limited to, spontaneous adverse event reports, clinical trial data, scientific literature, and non-clinical study results.

- Reason summary

  A brief summary of key data and rationale for further evaluation.

- Outcome, if closed

  State whether or not a specific action is required. Refer to the description of signal evaluation (to be described in the Section 3.16.2 of this guideline, Signal Evaluation) for further detail. Leave blank for signals under evaluation at the data lock point.

APPENDIX D – List of PBRER Sections, Identified as Providing Cumulative or Interval Information, and Ability to Share Modules with Other Regulatory Documents

		Cumulative	Interval	Potential shared module with
1	Introduction	X		
2	Worldwide Marketing Approval Status	X		E2F
3	Actions Taken in the Reporting Interval for Safety Reasons		X	Parts may be common to E2E and E2F
4	Changes to Reference Safety Information		X	
5	Estimated Exposure and Use Patterns			
5.1	Cumulative Subject Exposure in Clinical Trials	X		E2E and E2F
5.2	Cumulative and Interval Patient Exposure from Marketing Experience	X	X	E2E and E2F (cumulative only)
6	Data in Summary Tabulations			
6.1	Reference Information	Not applicable	Not applicable	
6.2	Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials	X		E2F
6.3	Cumulative and Interval Summary Tabulations from Post-marketing Data Sources	X	X	
7	Summaries of Significant Findings from Clinical Trials during the Reporting Period			

7.1	Completed Clinical Trials		X	E2F
7.2	Ongoing Clinical Trials		X	E2F
7.3	Long-term Follow-up		X	E2F
7.4	Other Therapeutic Use of Medicinal Product		X	E2F
7.5	New Safety Data Related to Combination Therapies		X	E2F
8	Findings from Non-interventional Studies		X	E2F
9	Information from Other Clinical Trials and Sources		X	E2F
10	Non-clinical Data		X	E2F
11	Literature		X	E2F
12	Other Periodic Reports		X	
13	Lack of Efficacy in Controlled Clinical Trials		X	E2F
14	Late-Breaking Information		X	E2F, if reports cover same period and submitted at same time
15	Overview of Signals: New, Ongoing, or Closed	X§	X	
16	Signal and Risk Evaluation			
16.1	Summary of Safety Concerns	X		
16.2	Signal Evaluation		X	
16.3	Evaluation of Risks and New Information	X	X	
16.4	Characterisation of Risks	X		
16.5	Effectiveness of Risk Minimisation (if applicable)		X	
17	Benefit Evaluation			
17.1	Important Baseline Efficacy/Effectiveness Information	X		
17.2	Newly Identified information on Efficacy/ Effectiveness		X	
17.3	Characterisation of Benefits	X	X	
18	Integrated Benefit-risk Analysis for Approved Indications			
18.1	Benefit-risk Context - Medical Need and Important Alternatives	X		
18.2	Benefit-risk Analysis Evaluation	X		
19	Conclusions and Actions	X	X	E2F
20	Appendices to the PBRER			

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§ At discretion of MAH.

APPENDIX E – Examples of Possible Sources of Information That May Be Used in the Preparation of the PBRER

Examples of potential sources of information to be used in preparation of a PBRER will be included in the Step 4 guideline as general guidance. Suggestions for information sources to be included in this list should be submitted during the consultation period.